PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
480102.411PC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 03/34655	31.10.2003	02.05.2003
International Patent Classification (IPC) or both national classification and IPC		
C07D207/12		
Applicant		
CARDIOME PHARMA CORP. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.11.2004	21.07.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Hanisch, I Telephone No. +49 89 2399-7880

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/34655

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-195 as originally filed

Claims, Numbers

1-100 as originally filed

Drawings, Figures

1-167 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1,5,7,9,13,15,17,21,23,29,31,33,37,39,53,55,57-67,69,70,72-84,86,87,89-100

   because:

   ☒ the said international application, or the said claims Nos. 53,55,57-67,69,70,72-84,86,87,89-100 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1,5,7,9,13,15,17,21,23,29,31,33,37,39 are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☒ the claims, or said claims Nos. 1,5,7,9,13,15,17,21,23,29,31,33,37,39 are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-100
	No:	Claims	
Inventive step (IS)	Yes:	Claims	37-50,84-100
	No:	Claims	1-36,51-83
Industrial applicability (IA)	Yes:	Claims	1-52,54,56,68,71,85,88
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III.

It is noted that the application refers to "prodrugs" and "metabolites". These terms are functional definitions which attempt to define a chemical compound in terms of a result to be achieved without giving a specific technical guidance for the selection of the suitable derivatives in the description and without proven general knowledge to show which derivatives in this specific case are suitable prodrugs. The term could be seen as a mere invitation to the skilled person to perform a research program in order to find the suitable variants. In such a situation, when the invention cannot be carried out over the whole claimed area without imposing an undue burden on the skilled person, the disclosure may be considered insufficient, even when simple in vivo or in vitro tests are available to determine whether or not a particular compound is covered by the claims. The search has therefore been restricted to the specific meanings of the the term "prodrug" which have been defined on page 108, i.e. to ester, amide and terminal peptide derivatives. This opinion exclusively relates to the searched subject-matter.

Claims 53,55,57-67,69,70,72-84,86,87,89-100 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims (Article 34(4)(a)(i)PCT).

Re Item V.

Relevant prior art is provided by
(A) WO 9950225
(B) WO 03105756
(B) as an intermediate document ist not regarded during the international phase, however, the current compounds appear to be a novel selection of the general formula given in (B). The exemplified compound of (B) falls within the part excluded from the current subject-matter by means of a proviso.

Novelty

The current compounds of formula (1A) appear to be a novel selection of (A) and

therefore satisfy Article 33(2) PCT.

Inventive Step

The problem underlying the present application appears to be the provision of further cyclohexylether derivatives which are useful for the treatment of arrhythmia etc. on acount of their ion channel modulating activity.

(A) appears to be the only relevant prior art. The current compounds fall within the general formula of (A), whereby the current examples appear to represent the specific structural combination of the two examples 6 and 24 of (A). Consequently, an inventive step in the sense of Article 33(3) PCT may only be acknowledged for those current compounds which show an unexpectedly improved effect. The therapeutic indices given in tables 4 and 5 may justify such an inventive step for the exemplified compounds compared to examples 6 and 24 of (A) (corresponding to examples 35 and 46 in table 5), and consequently for claims 37-50 and 84-100. However, the said effect may not be generalized over the whole claimed scope since it appears to be based on the said specific combination of substituents. Consequently, all compounds of claims 1-36 which do not fall within claims 37-50 and thus have not yet been shown to have an unexpectedly improved effect vis-à-vis the closest state of the art appear to be an obvious solution for the skilled person and thus lack an inventive step.

Industrial Applicability

For the assessment of the present claims 53,55,57-67,69,70,72-84,86,87,89-100 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.